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Crystal Structure of the Yersinia pestis GTPase Activator YopE

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Yersinia pestis, the causative agent of bubonic plague, evades the immune response of the infected organism by utilizing a type III (contact-dependent) secretion system to deliver effector proteins into the cytosol of mammalian cells, where they interfere with signaling pathways that regulate inflammation and cytoskeleton dynamics. The cytotoxic effector YopE functions as a potent GTPase activating protein (GAP) for Rho family GTP-binding proteins, including RhoA, Rac1 and Cdc42. Down-regulation of these molecular switches results in the loss of cell motility and inhibition of phagocytosis, enabling *Y. pestis* to thrive on the surface of macrophages. We have determined the crystal structure of the GAP domain of YopE (YopE-GAP; residues 90-219) at 2.2 Å resolution. Apart from the fact that it is composed almost entirely of alpha helices, YopE-GAP exhibits no obvious structural similarity with eukaryotic RhoGAP domains. Moreover, unlike the catalytically equivalent arginine fingers of the eukaryotic GAPs, which are invariably contained within flexible loops, the critical arginine in $YopE_{GAP}$ (Arg144) is part of an alpha helix. The structure of YopE-GAP is strikingly similar to the GAP domains from *Pseudomonas aeruginosa* (ExoS-GAP) and *Salmonella enterica* (SptP-GAP), despite the fact that the three amino acid sequences are not highly conserved. A comparison of the YopE-GAP structure with those of the Rac1/ExoS-GAP and Rac1/SptP complexes suggests that few, if any, significant conformational changes occur in YopE-GAP when it interacts with its G-protein targets. The structure of YopE-GAP may provide an avenue for the development of novel therapeutic agents to combat plague.